REMARKS

I. Amendments to the Title and Claims

The title and claims 23 and 73 have been amended solely to promote the allowance of the case and without acquiescing to the Examiner's rejection. The claims are supported by the originally filed specification, for example, page 5, lines 12-19, page 8, lines 3-12, page 9, lines 7-9 and page 20, lines 20-24, and canceled claims 28 and 75. No new matter has been added.

Claims 23, 29, 73 and 76 are pending. Applicant respectfully submits that the pending claims are allowable for the following reasons.

II. Arguments and Response to Rejections

The Written Description Rejections Should be Withdrawn

Claims 23 and 27-29 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. (Pages 3-4 of Office Action). The PTO contends that the term "blood-*borne* tumors" is new matter not supported by the specification because the specification discloses only "blood-*born* tumors such as leukemia"; and that the words "born" and "borne" have completely different meanings. *Id.* Applicant respectfully submits that such a rejection is improper, and respectfully disagrees with the rejection.

The PTO alleges that the word "*born*" means "deriving or resulting from," while the word "*borne*" means "transported or transmitted by" in their dictionary definitions; and that the specification discloses only the use of thalidomide to treat "blood-*born* tumors such as leukemia" but not "blood-*borne* tumors." (Page 4 of Office Action). Applicant respectfully disagrees. First, Applicant believes that "blood-*born* tumors" and "blood-*borne* tumors" are synonymous, and there is no distinction made by Applicant, nor those skilled in the art with respect to these two spellings. Contrary to the PTO's contention, the term "blood-*borne* tumors" is used to designate hematologic malignancies such as multiple myeloma and leukemia. *See* Exhibits 1 and 2. Persons skilled in the art use the term "blood-*borne* tumors" to refer to hematologic malignancies. *Id.* In other words, the specification, which discloses the use of thalidomide to treat "blood-*born* tumors," conveys with reasonable clarity to those skilled in the art that applicant was in possession of the invention for the use of thalidomide in treating "blood-*borne* tumors." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ 2d 1111, 1117 (Fed. Cir. 1991). The claims reciting either "blood-*borne* tumors" or

"blood-*born* tumors" are adequately supported within the meaning of the written description requirement of 35 U.S.C. § 112.

Also, it is admitted by the PTO that one skilled in the art and the examiner interpret "blood-*borne* tumors" to mean hematological malignancies such as leukemia and that leukemia is described as "blood-*borne* tumors" in the specification. See page 5 of Office Action dated June 12, 2008.

Nevertheless, solely to promote the allowance of the case and without acquiescing to the Examiner's rejection, title and claims 23 have been amended by changing "blood-borne tumors" to "blood-born tumors" because the specification uses the term. Thus, this rejection is moot and should be withdrawn.

Next, claims 23, 27-29 and 73-76 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. (Pages 4-5 of Office Action). The PTO contends that the term "therapeutically effective amount of thalidomide" is new matter not supported by the specification, because the specification discloses only "dosage sufficient to inhibit angiogenesis, and there is no support for the claimed "therapeutically effective amount of thalidomide" for treating blood-borne tumors. *Id.* Applicant respectfully disagrees with the rejection.

Applicant respectfully submits that, contrary to the PTO's allegation, the use of the term "therapeutically effective amount" clearly refers to the amount of thalidomide used in treating blood-borne or blood-born tumors, particularly when read in light of the specification. For example, the specification at page 5, lines 12-19 states as follows:

> "It should be noted that angiogenesis has been associated with blood-born tumors such as leukemias, any of various acute or chronic neoplastic diseases of the bone marrow in which unrestrained proliferation of white blood cells occurs, usually accompanied by anemia, impaired blood clotting, and enlargement of the lymph nodes, liver, and spleen. It is believed that angiogenesis plays a role in the abnormalities in the bone marrow that give rise to leukemia-like tumors."

Also, the specification at page 9, lines 7-9 states as follows:

> "It is yet another object of the present invention to provide a method and composition for the treatment of blood-born tumors such as leukemia."

Furthermore, the specification provides sufficient explanation as to what "therapeutically effective amount" may be. For example, the specification at page 5, lines 10-12 states "in a dosage sufficient to inhibit angiogenesis"; and the specification at page 20, lines 20-24 sates "for oral administration to humans, a dosage of between approximately 0.1

to 300 mg/kg/day, preferably between approximately 0.5 to 50 mg/kg/day, and most preferably between approximately 1 to 10 mg/kg/day is generally sufficient."

Clearly, based on those disclosures, those skilled in the art would have understood what "therapeutically effective amount" means. The specification has sufficiently described that "therapeutically effective amount" refers to the amount of thalidomide to be used in treating blood-born or blood-borne tumors. Applicant was clearly in possession of the invention as of the filing date of this application.

Nevertheless, solely to promote the allowance of the case and without acquiescing to the Examiner's rejection, claims 23 and 73 have been amended by changing "a therapeutically effective amount" to "in an amount between approximately 0.5 and approximately 50 mg/kg/day," as recognized by the Examiner (page 4 of Office Action) and described in the specification (page 20, lines 20-24). Thus, this rejection is moot and Applicant respectfully requests that the rejection be withdrawn.

The Claims are Enabled

On pages 5-12 of the Office Action, claims 23 and 27-29 are rejected as allegedly failing to comply with the enablement requirement under 35 U.S.C. §112, first paragraph. Specifically, based on an analysis of the factors set forth in *In re Wands* ("*Wands* factors"), the PTO alleges that the specification, while being enabling for treating multiple myeloma and leukemia, does not provide enablement for treating blood-*borne* tumors. *Id.* Applicant respectfully traverses this rejection.

It appears that the rejection is based on the allegation that the whole scope of the limitation "blood-*borne* tumors" is not enabled on the ground that blood-*borne* tumors are different from "blood-*born* tumors." Although Applicant strongly disagrees and submits that "blood-borne tumors" and "blood-*born* tumors" are interchangeably used to designate hematologic malignancies such as multiple myeloma and leukemia, the claims are amended to recite the treatment of "blood-*born* tumors" to be consistent with the disclosure of the specification.

In fact, the PTO admitted enablement for "blood-*born* tumors." In the Office Action, pages 5 and 11, the PTO acknowledges that the specification enables for treating multiple myeloma. Also, the PTO acknowledges that the specification discloses the use of thalidomide to treat blood-born tumors such as leukemia. (Page 4 of Office Action). Claims 73-76 reciting leukemia are not rejected as lacking enablement requirement. (Page 5 of

Office Action). Thus, the rejection is moot and Applicant respectfully requests that the rejection be withdrawn.

Further, Applicant respectfully submits that the treatment of blood-born tumors is enabled for the following reasons. While the Examiner relies heavily on certain references that purportedly show that thalidomide is ineffective in treating certain cancers, such disclosures in prior art, even if taken as true[1], cannot form a basis to rebut the presumption of enablement. As the Federal Circuit explained, although the question whether or not a reference "teaches away" from a claimed invention is relevant in determining obviousness, "[it is] not the primary [question] bearing on enablement." *Singh v. Brake*, 317 F.3d 1334, 65 U.S.P.Q.2d 1641 (Fed. Cir. 2003) (emphasis added).

Because the fact that thalidomide inhibits angiogenesis was not known until the discovery of the present inventor, the claimed invention is distinct from the references cited by the Examiner. After the present inventor reported that thalidomide inhibits angiogenesis and that there are clear implications for treating tumors, thalidomide had been being studied and used for treating tumors. *See, e.g.*, previously submitted Diggle (page 630, left column, the second paragraph); Kumar (page 2478, the second paragraph); Rajkumar (page 900, the last two paragraphs); Singhal *et al.* (page 1565, 2nd paragraph of right column); Kneller A. et al. (page 393, left column); Hideshima T. et al. (page 2943, left column); and Barlogie B. et al. (pages 492-3). These post publications support that a skilled person in the art can practice the claimed invention without undue experimentation based upon the disclosure of the specification.

Also, it is well settled that data provided subsequent to the filing of an application should be considered "to substantiate any doubts" with regard to enablement issues. *In re Brana*, 51 F.3d at 1566-67; see also MPEP §2164.05. Such data "goes to prove that the disclosure was in fact enabling when filed." *Id.* Applicant submits that the fact that the treatment of blood-born tumors using thalidomide is enabled is well documented.

Applicant submitted many articles to support that thalidomide is effective in treating blood-born or blood-borne tumors such as multiple myeloma, leukemia and lymphoma[2]. For

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[1] Applicant by no means concedes that thalidomide is ineffective in treating cancer. Quite to the contrary, there are numerous references in the record that show that thalidomide is indeed effective in treating cancer such as multiple myeloma.

[2] These articles were discussed and submitted to the Examiner at the interview on March 7, 2008, and described in the response filed on March 14, 2008 and list of references cited in IDS. All these references were considered by the examiner and made of record in the file history of this application (C318-C334).

example, Applicant submitted Furman *et al.*(*Abstract #6640*, 2005 and *Abstract* #4835, 2004) reporting on the study of thalidomide in treating patients with chronic lymphocytic leukemia (CLL); Steins *et al.* (*Blood*, 2002; *Leukemia & Lymphoma,* 2003; and *European Journal of Hematology*, 2007) describing that thalidomide has anti-angiogenic effects and is effective in treating patients with acute myeloid leukemia (AML); and Strupp *et al.* (*Leukemia Research,* 2005) reporting on study of patients with hairy cell leukemia (HCL) using thalidomide and the role of angiogenesis in the blood-borne tumors.

For effectiveness of thalidomide in treating patients with lymphoma, Applicant submitted Ruan *et al.* (*Abstract* #2751, 2006), Damaj (*Leukemia*, 2003) and Goy (*Clinical Lymphoma & Myeloma,* 2006) which describe that targeting angiogenesis is a novel therapeutic strategy in lymphoma, and thalidomide is effective in treating patients with mantle cell lymphoma (MCL); Game *et al.* (*Abstract* #5235, 2001) report on treating patients with non-Hodgkin's lymphoma (NHL); Larson *et al.* (*Clinical Advances in Hematology & Oncology*, 2005) report on patients with HIV-related lymphoma; and Ramasamy *et al.* (*Haematologica*, 2006) report on patients with angioimmunoblastic T-cell lymphoma.

Also, Folkman (*Nature Review*, 2007) discusses that angiogenesis has an essential role in tumor formation; that understanding angiogenesis process and angiogenesis inhibitors are important for treatments of cancers; and that angiogenesis inhibitor thalidomide was approved for treating multiple myeloma and was being studied for patients with various tumors such as NHL, AML, CLL and leukemias (page 276). Thomas *et al.* (*Current Opinion in Oncology* 2000) and Brennen *et al.* (*Clinical Prostate Cancer* 2004) also describe that angiogenesis plays an important role in haematological malignancies; that thalidomide has an inhibitory effect on angiogenesis as shown in an animal model by the present inventor D'Amato; and that thalidomide could play a significant role in treating haematological malignancies through anti-angiogenic activity.

Therefore, the articles Applicant provided establishes the efficacy of thalidomide in treating blood-borne or blood-born tumors. These publications evidence that a skilled in the art can use and practice the claimed invention for treating blood-born tumors in a human using thalidomide, based on the disclosure of the specification. As such, the treatment of blood-born tumors as claimed is adequately enabled in this application.

Nonetheless, the Office Action alleges that the working examples in the specification are limited to demonstrating the anti-angiogenic activity of thalidomide in animal models of angiogenesis, but there are no *in vitro* or *in vivo* experimental models of any diseases described, including cell proliferation or animal tumor models (Office Action, pages 10-11).

Applicant respectfully submits that contrary to the allegations, the *in vivo* data in the specification reasonably correlates with the claimed invention. Example III of the specification discloses the *in vivo* inhibition of bFGF induced corneal neovascularization by thalidomide. (Specification, pages 26-27). Specifically, the specification discloses that treatment with a dose of 200 mg/kg of thalidomide resulted in an inhibition of the area of vascularized cornea that ranged from 30-51% in angiogenesis assays with a median inhibition of 36%.[3] (Specification, page 27 and Figures 6-7). "[A]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a working example if that example correlates with a disclosed or claimed method invention." *In re Brana*, at 1566; MPEP §2164.02. "A rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence." *See Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985).

Further, the specification (page 5, line 12 to page 6, line 3) clearly describes that blood-born tumors are associated with angiogenesis and that inhibition of angiogenesis would lead to the treatment of blood-born tumors in humans. MPEP §2164.04, *citing in re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367 (CCPA 1971) (A specification disclosure is "presumptively accurate") (emphasis added)). With the response filed on October 31, 2007, Applicant also submitted publications to show the correlation between the methods for inhibiting the growth of tumors in humans and the animal models for angiogenesis inhibition described in the specification. *See e.g.*, Langer *et al.*, Gimbrone *et al.*, "Tumor Growth and Neovascularization: An Experimental Model Using the Rabbit Cornea," *J. Natl. Cancer Inst.* (1974) 52(2): 413-427, and D'Amato *et al.*, "Thalidomide is an Inhibitor of Angiogenesis," *Proc. Natl. Acad. Sci., U.S.A.* (1994) 91: 4082-4085.

Further, by the priority date of this application, it had become the established consensus among those skilled in the art that tumors need angiogenesis to grow. For example, in 1971, Dr. Judah Folkman published a paper that tumor growth is angiogenesis-dependent in the New England Journal of Medicine (1971, 285: 1182-1186) entitled *"Tumor angiogenesis: therapeutic implications."* *See* Exhibit 3. Also, Applicant submits an article which evidences that angiogenesis and blood-born tumors (leukemia, multiple myeloma, and lymphoma) are inextricably linked. *See* Exhibit 4, Cancer Medicine, page 48, the passage headed *"Hematologic malignancies are angiogenic."* A copy of the *"The Angiogenesis Foundation"* website provides a summary of the history of angiogenesis-based research and

[3] As pointed out in Applicant's response filed October 31, 2007, the rabbit cornea assay of Example III is a well-known and accepted animal model for the determination of a drug's effect on angiogenesis.

details further relevant references that angiogenesis is a common denominator in all cancers. *See* Exhibit 5. Thus, by the priority date of the application, those skilled in the art recognize that compounds able to inhibit angiogenesis would be useful in the treatment of blood born tumors, and subsequently published articles serve to confirm the accuracy of this view.

Thus, Applicant respectfully submits that the examples in the specification, in effect, constitute working examples for the claimed invention. *In re Brana*, at 1566; MPEP § 2164.02.

Nonetheless, the Office Action alleges that the specification provides no reasonable guidance for specific administration regimens (e.g. timing, dosages, etc.) necessary to prevent or inhibit the growth of any specific tumors.[4] (Office Action, pages 11-12). Applicant respectfully traverses this rejection.

Applicant respectfully submits that the specification does provide sufficient guidance to enable one of skill in the art to practice the claimed invention. Specifically, dosages, routes of administration, and formulations are provided on page 20 of the instant specification. With regard to screening for effective dosages for the treatment of a disorder in a human, the Board of Patent Appeals and Interferences in *Ex parte Skuballa* stated:

> While some experimentation may be required to determine optimum dosages...such experimentation is not considered undue...We are satisfied that the skilled worker in this art could readily optimize effective dosages and administration regimens... As is well known, the specific dosage for a given patient under specific conditions and for a specific disease will routinely vary, but determination of the optimum amount in each case can readily be accomplished by simple routine procedures.

(12 U.S.P.Q.2d 1570 (Bd. Pat. App. & Interf. 1989)) (emphasis added).

Thus, to the extent the PTO is basing the rejection under 35 U.S.C. §112 on the need for screening, Applicant respectfully submits that such a rejection is improper. One skilled in the art would have been able to practice the claimed invention by administering the specified amount of thalidomide using the specified routes of administration to patients having blood-born tumors, as provided on page 20 of the instant specification, and in view of the clear descriptions of the relationship between the inhibition of angiogenesis and the tumors in humans in the specification.

In sum, Applicant respectfully submits that the specification provides sufficient information and guidance to those of ordinary skill in the art to make and use the claimed invention, and that to the extent any experimentation is necessary, such experimentation is

[4] The lack of clinical or human data is not a proper basis for an enablement rejection.

not undue. Therefore, Applicant respectfully requests that the rejection of the claims under 35 U.S.C. § 112, first paragraph be withdrawn.

The Rejection Under 35 U.S.C. §103 Should be Withdrawn

Claims 23, 27-29 and 73-76 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Vogelsang *et al.* (*N. Engl. J. Med.*, 1992, vol. 326, pages 1055-1058, "Vogelsang *et al.*") in view of Kaplan (US Patent No. 5,385,901, "Kaplan"). (Office Action, pages 13-14). The PTO alleges that Vogelsang *et al.* discloses the administration of thalidomide to patients with chronic graft-versus-host disease whose primary diagnosis was chronic myelogenous leukemia (Table 1), and thus the reference teaches the administration of thalidomide to patients having blood-borne tumors and leukemia. Page 13 of the Office Action. Applicant respectfully traverses this rejection.

The pending claims as amended recite, *inter alia,* a method of treating patients having blood-born tumors by administering a thalidomide capsule. Vogelsang *et al.* reported on studies of thalidomide in treating patients with chronic graft-versus-host disease, not treating blood-born tumor patients (see Table 3, page 1057). Vogelsang *et al.* does not teach or suggest any uses of thalidomide for treating patients with blood-born tumors or leukemia, as recited in the instant claims. Vogelsang *et al.* is silent as to treating blood-born tumors with thalidomide capsule, as recited in the pending claims. Indeed, Vogelsang *et al.* teaches away from the claimed invention by not disclosing the use of thalidomide for treating cancer but focusing only on treating chronic graft-versus-host disease.

Applicant respectfully submits that the reference must be read in view of the other art that teaches away from the claimed invention. Indeed, the PTO admitted, in pages 7-9 of Office Action, that the references cited by the Examiner support that thalidomide is not effective in treating tumors, and that the references cannot render obvious the claimed invention because there would be no reasonable predictability or expectation of success. For purpose of obviousness analysis, a prior art that teaches away negates an obviousness rejection. "[A]n applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." In *re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003). (Emphasis added.) Thus, Applicant respectfully submits that the instant claims are not obvious over the cited references.

Nevertheless, the Office Action states (1) that Kaplan teaches that thalidomide is useful in controlling abnormal concentrations of TNF-α; (2) that it would have been obvious to one of ordinary skilled in the art to administer thalidomide via known administration routes

as thought by Kaplan. (pages 13-14 of Office Action). Applicant respectfully disagrees.

Kaplan relates to the use of thalidomide for controlling abnormal concentrations of TNF-α in Cachexia, septic shock and HIV infection (Abstract and Column 3). It does not disclose or suggest that thalidomide is used for treating cancer, much less blood-born tumors or leukemia. Further, Kaplan teaches away from the treatment of the recited tumors by focusing on the use of the compound for treating the different diseases. Indeed, Kaplan discloses that TNF-α is associated with the destruction of tumor cells as its name suggests (Column 2, lines 60-62). Thus, a person skilled in the art would not have been motivated to use thalidomide that inhibits the TNF-α production as taught in Kaplan, for treating tumors, much less blood-born tumors, as in the claimed invention.

In view of the foregoing, from any references cited by the Examiner, alone or in combination, one of skill in the art would have had no reason to use thalidomide capsule for treating blood-born tumors, to arrive at the instant claims. Thus, Applicant respectfully submits that the instant claims are not obvious over the cited references.

Further, the combined teachings do not provide the legally required reasonable expectation of success. When the references are combined, one skilled in the art is merely taught that thalidomide may be used for treating chronic graft-versus-host disease, Cachexia, septic shock and HIV infection as disclosed in Vogelsang *et al.* or Kaplan, but not for treating any cancers, because the references do not teach that thalidomide was effective in treating cancers, much less blood-born tumors. As such, the art does not provide any reasonable expectation that thalidomide could be successfully used in treating blood-born tumors. In other words, the cited art does not provide any "direction as to which of many possible choices is likely to be successful." This is precisely what the courts have held not to be a reasonable expectation of success. (*Medichem, S.A. v. Robaldo,* 437 F.3d 1157, 1165 (Fed. Cir. 2006); *O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)). Thus, Applicant respectfully submits that the instant claims are not obvious over the cited references, and requests that this rejection be withdrawn.

III. Conclusion

Applicant respectfully requests that the above amendment and remarks be entered in the file of this application. Should the Examiner not agree that all claims are allowable, then a further personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application. Please charge any required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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